

May 12, 1947.

Dr. R.G. Meader,
Jane Coffin Childs Memorial Fund,
333 Cedar Street,
New Haven, Connecticut.

Dear Dr. Meader-

In conformance with our conversation last week, I am incorporating into this letter a prospectus of my plans for 1947-48, which I should appreciate your sending to the Board of Scientific Advisers. I am appending also a preliminary summary of the work that I have done thusfar.

Preliminary Progress Report

In spite of the fact that bacteria provide unexampled material for the study of genetic changes (mutation studies), geneticists have been understandably loath to homologize the results of researches on this group of organisms with those on other plants and animals, largely because it has been thought that a formal genetic analysis by hybridization methods was impossible. The research performed in this laboratory with Prof. E.L. Tatum, under the auspices of the Childs Fund has elicited evidence that there is indeed a sexual phase in some strains of the bacterium Escherichia coli, and that the inheritance of several mutant biochemical characters obeys Mendelian laws. There is now no reason therefore why mutations in bacteria should not be classified along with mutations in other organisms. The purely genetical investigations have shown that there is probably only a single linkage group (or chromosome) in this bacterium.

Advantage is being taken of the opportunity afforded by this material to study the inheritance of resistance to bacteriophages

and to deleterious chemical substances; the analysis is not yet complete but the data are adequate to show that there is a relatively simple mutational basis for the development of resistance to these agents. Materials are also being accumulated which promise to lead to an interesting study of the process of mutation, which I hope to engage in next year. For example a system has been found in which mutations both to and away from a functioning condition of a gene can be readily enumerated. In another system, diverse strains have been found in which the rates of mutation of a gene are widely different.

A third aspect of these investigations has concerned the study of other organisms to determine whether a sexual phase can be detected in them. This attempt has so far been fruitless, but the investigation is still incomplete.

In addition to those publications of which reprints are already on file, this research has led to the following publications, either in press or in an advanced stage of preparation:

1. Lederberg, J. The Nutrition of Salmonella Arch. Bioch. in press.
2. Lederberg, J. and E.L. Tatum, New Genotypes in mixed cultures of biochemical mutants of E. coli Cold Spring Harbor Symposium, 1946, in press.
3. Tatum, E.L. and J. Lederberg, Gene Recombination in the bacterium Escherichia coli. Jour.Bact. in press.
4. Lederberg, J. Problems in Bacterial Genetics in manuscript
5. Lederberg, J. and E.L. Tatum, The segregation of genetic factors in Escherichia coli. in draft manuscript.

Research Plans

The research program which I have in mind is perhaps already implicit. Dr. Ryan and I have long planned to use biochemical mutants of bacteria for an intensive study of the mutation process; this will be particularly relevant now that genetic analysis is possible. This program includes comparisons of the effects of radiations, temperature, carcinogenic and other chemical mutagens primarily on the reverse-mutation of biochemical deficiency mutations to the normal functioning state, but in a few instances, also in the mutational loss of function. The implications of 'reverse-mutations' for cancer have already been mentioned in a note entitled "A nutritional concept of cancer", but these investigations must be regarded as valuable in themselves as attempts to improve our knowledge of the gene. Bacteria are unprecedentedly suitable for this type of research. The discovery of genetically conditioned differences in mutability may open up an additional avenue of research.

For the support of the program just summarized of research and medical studies, I do hereby appeal to the Board for a renewal of the fellowship grant, for the present enjoyment of which I am most grateful.

Yours sincerely,

Joshua Lederberg.

Plans for 1947-1948

By September 1947, all the requirements for the degree of Ph.D. at Yale University shall have been completed, my preparation for this degree having consisted almost entirely of the research which has been sponsored by the Childs Fund. At that time, I propose to return to the College of Physicians and Surgeons, Columbia University, to resume and complete studies leading to the degree of M.D. My place in the third-year class has been assured. There has been almost complete unanimity among the people whom I have consulted regarding these plans advising that the completion of these studies would be an exceedingly valuable preparation for later research in the medical sciences, particularly in such a field as cancer where there must be a close collaboration between biological and clinical studies.

On the basis of my previous experiences, however, I can assure the Board that I will also be able to continue to pursue researches in the directions that were begun under the current fellowship grant. I can anticipate that I shall be able to devote approximately one-third of my attentions to this purpose. During my first two years, I was able to do even more, but the increasing burdens of the later clinical years must be taken into account. The fundamental methods and techniques and materials that will be used have been developed already here, so that I shall be able to spend what time I have on their application. My wife is trained in this field and will be able to assist me, although she expects to be pursuing her own studies at Columbia. The space and major facilities for the proposed work have been promised to me in the laboratory of Dr. F.J. Ryan of the department of Zoology, Columbia University, with whom I have had the pleasure of collaborating in the past.